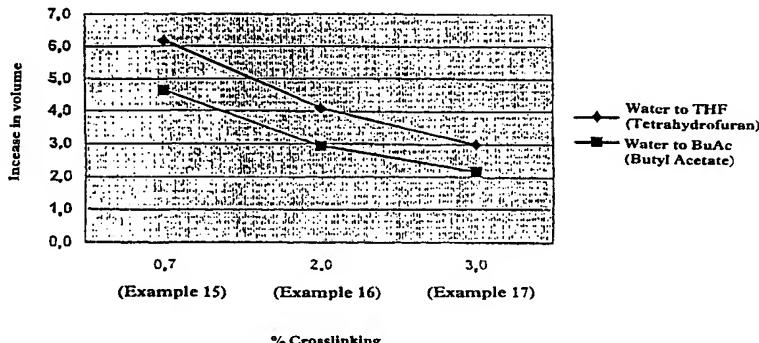




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : <b>C08F 257/02, 265/04, 291/00</b>		A1	(11) International Publication Number: <b>WO 00/61647</b> (43) International Publication Date: 19 October 2000 (19.10.00)
<p>(21) International Application Number: <b>PCT/GB00/01334</b></p> <p>(22) International Filing Date: 10 April 2000 (10.04.00)</p> <p>(30) Priority Data: 9908163.0 9 April 1999 (09.04.99) GB 0007008.6 22 March 2000 (22.03.00) GB</p> <p>(71) Applicant (for GB only): COCKBAIN, Julian [GB/GB]; Frank B. Dehn &amp; Co., 179 Queen Victoria Street, London EC4V 4EL (GB).</p> <p>(71) Applicant (for all designated States except US): DYNO SPECIALTY POLYMERS AS [NO/NO]; Svelleveien, N-2001 Lillestrom (NO).</p> <p>(71) Applicants (for US only): BERGE, Arvid, Trygve (heir of the deceased inventor) [NO/NO]; Falsens gate 14, N-7052 Trondheim (NO). UGELSTAD, Viola (heiress of the deceased inventor) [NO/NO]; Kongensgate 84, N-7012 Trondheim (NO).</p> <p>(72) Inventors: ELLINGSEN, Turid (deceased).UGELSTAD, John (deceased).</p>		<p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): JØRGEDAL, Arne [NO/NO]; Skolevegen 10, N-2005 Raelingen (NO). AKSNES, Elin, Marie [NO/NO]; Syrenveien 1, N-0870 Oslo (NO). FONNUM, Geir [NO/NO]; Asbjørnsensvei 40, N-1476 Rasta (NO). MOLTEBERG, Astrid, Evenrød [NO/NO]; Ospelia 6, N-1900 Fettsund (NO). NORDAL, Rolf [NO/NO]; Snekkerstuveien 32, N-2020 Skedsmokorset (NO). PETTERSEN, Henning [NO/NO]; Kirkegate 33, N-2000 Lillestrøm (NO). TAARNEBY, Tollef [NO/NO]; Jerpeveien 17, N-1929 Auli (NO). STAALE, Solveig, Marie [NO/NO]; Østlifaret 42, N-1476 Rasta (NO). WENG, Ellen [NO/NO]; Østlagtveien 3, N-1415 Oppgård (NO). HANSEN, Finn, Knut [NO/NO]; Nygaten 17, N-2010 Strømmen (NO). NORDBØ, Silje, Steinbakk [NO/NO]; Ullevålsveien 56D, N-0454 Oslo (NO). AUNE, Oddvar, Arfmenn [NO/NO]; Okstadplassen 25, N-7075 Tiller (NO). BERGE, Arvid, Trygve [NO/NO]; Falsens gate 14, N-7052 Trondheim (NO). BJØRGUM, Jon, Olav [NO/NO]; Ørgeilan 7, N-7089 Heimdal (NO).</p> <p>(74) Agents: COCKBAIN, Julian et al.; Frank B. Dehn &amp; Co., 179 Queen Victoria Street, London EC4V 4EL (GB).</p> <p>(81) Designated States: AE, AG, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), DM, DZ, EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR (Utility model), KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p>	
<p><b>Published</b> With international search report.</p>			

(54) Title: PROCESS FOR THE PREPARATION OF MONODISPERSE POLYMER PARTICLES



## (57) Abstract

A process for the preparation of monodisperse polymer particles which are formed by contacting monomers with aqueous dispersions comprising monodisperse swellable seed polymers/oligomers, and initiating polymerisation in the presence of a steric stabiliser. The resulting swollen seed particles are characterised by the particle mode diameter.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

Process for the preparation of  
Monodisperse Polymer Particles

5

This invention relates to improvements in and relating to the preparation of substantially monodisperse polymer particles.

Monodisperse polymer particles (i.e. particles with a coefficient of variation of less than 10%, preferably less than 5% and more preferably less than 3%) have been commercially available for several years and find applications in many technical fields, e.g. in pharmaceuticals, in separation processes, as toners, as filters, as spacers, etc.

Polymer beads may be produced by diffusing a monomer and a polymerization initiator (or catalyst) into polymer seeds in an aqueous dispersion. The seeds swell and following initiation of polymerization, e.g. by heating to activate the initiator, larger polymer particles are produced. The maximum volume increase due to swelling and polymerization is about x5 or less. The late Professor John Ugelstad found that the capacity of the seeds to swell could be increased to a volume increase of x125 or even more if an organic compound with relatively low molecular weight and low water solubility is diffused into the seeds before the bulk of the monomer is used to swell the seeds. The effect is based on entropy and not particularly in the chemical nature of the organic compound. Conveniently the polymerization initiator may be used for this purpose. Organic solvents, e.g. acetone or a relatively small portion of the monomer, may be used to enhance diffusion of the organic compound into the seeds. This "Ugelstad polymerization process", which is described for example in EP-B-3905 (Sintef) and US-A-4530956 (Ugelstad), may be used to produce monodisperse particles, if necessary

- 2 -

carrying out several swelling and polymerization stages to reach the desired particle size.

WO 92/16581 (Cornell Research Foundation) also describes the preparation of monodisperse particles, particularly macroporous polymer beads. The process described uses a three phase emulsion containing soluble polymer particles, a monomer phase, and water. The three phase emulsion also includes an emulsifier and a suspension stabiliser. The polymer particles undergo swelling absorbing the monomer which is then polymerized. In this process the soluble polymer seed particles act as both shape/size regulators and as a porogen. The initial (i.e. before swelling) particles have a diameter of from about 0.5 to 10  $\mu\text{m}$ , 2 to 5  $\mu\text{m}$  being most preferred, and are produced by conventional techniques, such as emulsion or dispersion polymerization.

In a simplified version of the Ugelstad process the enhanced capacity for swelling may be achieved simply by the use of oligomeric seed particles, e.g. where the oligomer weight average molecular weight corresponds to up to 50 monomer units or up to 5000 Dalton.

The processes described in EP-B-3905 and US-A-4530956 (the disclosures of which are hereby incorporated by reference) and the simplified Ugelstad process are relatively complex and inefficient. The processes described in WO 92/16581 do not especially improve upon those disclosed in EP-B-3905 and US-A-4530956. The essence of WO 92/15681 would appear to be the production of macroporous polymer beads of substantially uniform size, the macroporosity being achieved through extraction of the (initially) soluble polymer from the resultant insoluble expanded beads. It is well known in the art that addition of steric stabilizers to dispersion polymerizations of polymer seeds can be useful in controlling size of beads; this feature of WO 92/16581, therefore, appears to represent

- 3 -

nothing more than the arbitrary introduction of an obvious and well-known advantageous process feature into the process of the invention.

5 There is a need for improvements to all these processes, in particular improvements which make it easier to produce monodisperse polymer particles with different chemical or physical characteristics.

10 It is important to use a polymeric steric stabilizer in the aqueous phase in order to avoid agglomeration of desired-sized particles and formation of undersized particles in the polymerization stage. Surprisingly it has been found that where the swelling generates particles below 25 $\mu$ m in size undersized particle formation is essentially avoided by the use of 15 polyvinylpyrrolidone (PVP) as a steric stabilizer whereas where the swelling generates particles above 5 $\mu$ m in size cellulose ethers function effectively as steric stabilizers. While PVP can be used to stabilize particles above 16 $\mu$ m it is especially preferred for use 20 with particles up to 16 $\mu$ m.

Thus viewed from one aspect the invention provides a process for the preparation of monodisperse polymer particles which process comprises:

1) either

25 (a) forming an aqueous dispersion comprising (i) monodisperse swellable seed polymer (or oligomer) particles, (ii) droplets comprising an organic compound (e.g. a polymerization initiator) with a molecular weight below 5000 Dalton and a water solubility at 25°C of less than 10<sup>-2</sup>g/L, (iii) an anionic surfactant, and, 30 optionally, (iv) an organic solvent in which said organic compound is soluble,

and (b) allowing said organic compound to diffuse into said seed particles

35 or (a) forming an aqueous dispersion comprising monodisperse swellable seed oligomer particles and preferably an anionic surfactant;

- 4 -

2) contacting the aqueous dispersion of seed particles with a monomer which, where said organic compound is present, is at least ten times more water soluble than said organic compound, and if required a water-soluble steric stabilizer, if required a porogen, and if required a polymerization initiator, and allowing said monomer to diffuse into said seed particles to form an aqueous dispersion of swollen seed particles; and

3) initiating polymerization of said monomer in an aqueous dispersion of swollen seed particles, characterised in that

where the mode diameter of said swollen particles is greater than  $5\mu\text{m}$  then the aqueous phase of said aqueous dispersion of swollen seed particles during polymerization further contains as a steric stabilizer a water soluble cellulose ether

or in that where said mode diameter of said swollen particles is in the range 1 to  $25\mu\text{m}$  the aqueous phase of said aqueous dispersion of swollen seed particles during polymerization further contains as a steric stabilizer polyvinylpyrrolidone.

Alternatively, the process feature 2) above may instead involve contacting the aqueous dispersion of seed particles with a monomer which, where said organic compound is present, is at least ten times more water soluble than said organic compound, and allowing said monomer to diffuse into said seed particles to form an aqueous dispersion of swollen seed particles, and if required adding a water-soluble steric stabilizer, if required adding a porogen, and if required adding a polymerization initiator.

In the above process, the mode diameter of said swollen particles is preferably more than  $15\mu\text{m}$  where the aqueous phase of said aqueous dispersion of swollen seed particles during polymerization further contains as a steric stabilizer a water soluble cellulose ether.

Where water soluble cellulose ethers are used when

- 5 -

forming the swollen particles, the mode diameter of the swollen particles will preferably be less than 200  $\mu\text{m}$ .

The PVP preferably has a weight average molecular weight of 10 to 2000 kD, more preferably 25 to 1500 kD, especially 30 to 1000 kD. Where the swollen particles have sizes at the lower end of the 1 to 25  $\mu\text{m}$  range it is preferred to use lower molecular weight PVP and where the swollen particles have sizes at the upper end of that range it is preferred to use higher molecular weight PVP. Thus for example 20 to 80 kD, e.g. 30 kD PVP is particularly suitable for swollen particle sizes of up to 8  $\mu\text{m}$  while 900 to 1500 kD PVP is particularly suitable for swollen particle sizes above 8  $\mu\text{m}$ . Examples of suitable such PVP include PVP K30 and PVP K90 (available for example from International Speciality Products and from Fluka).

Examples of suitable cellulose ethers include alkyl celluloses, preferably  $\text{C}_{1-4}$ -alkyl celluloses; and (hydroxyalkyl)alkyl celluloses, preferably (hydroxy- $\text{C}_{1-4}$ -alkyl) $\text{C}_{1-4}$ -alkyl celluloses, more preferably (hydroxy- $\text{C}_{1-4}$ -alkyl)methyl celluloses. Typically, these cellulose ethers have weight average molecular weights in the range 10 to 100 kD, especially 15 to 80 kD. Such materials are available commercially in a range of different degrees of substitution and molecular weight, e.g. as Benecel MP 333C, Benecel MP 651C, Culminal MHPC 1500, Culminal MHPC 400, Walocel MK 400 PFV and Methocel K100. Cellulose ethers which generate a viscosity when in 2% aqueous solution at 21°C of 50 to 150 mPa.s are especially preferred.

In the present invention, the size increase by volume (i.e. the ratio of the volume of the swollen particles to the volume of the seed particles) is between 30 and 1000 times. It is a preferred embodiment that the corresponding ratio with regard to the increase in diameter is not less than 3.5.

- 6 -

It should be noted that the process steps recited above may represent the final swelling and polymerization stage or an intermediate swelling and polymerization stage in an Ugelstad polymerization process for preparing monodisperse polymer particles.

The mixture which comprises the monomer (or mixture of monomers) is preferably in the form of an aqueous dispersion when it is contacted with the polymer particles. Where a polymerization initiator is contacted with the aqueous dispersion of polymer particles this too is preferably in the form of an aqueous emulsion, preferably also containing a polymerizable or non-polymerizable organic solvent, e.g. alcohols (particularly C<sub>1-4</sub> alkanols), ethers (especially cyclic ethers), ketones (e.g. acetone), dialkylsulphoxides, dialkylformamides, monomers, etc. Water miscible solvents, such as acetone, are however preferred. The droplet size of both such emulsions is preferably below 5μm, e.g. 0.1 to 1μm, particularly 0.3 to 0.6μm. This may be produced using an intensive mixer, e.g. a pressure homogenizer (such as a Gaulin homogenizer) or a rotor stator mixer. The steric stabilizer, if present, may be added in whole or in part, together with the monomer, to the aqueous dispersion of seed particles; if additional steric stabilizer is required this is preferably added in aqueous solution form. The steric stabilizer concentration in the polymerization medium is preferably 1 to 40 g/L, especially 4 to 25 g/L, for polyvinylpyrrolidone and 0.1 to 10 g/L, especially 1 to 5 g/L, for cellulose ethers.

Figure 1 shows the degree of swelling (by volume) of dispersed particles produced in Examples 15-17, from water to THF and from water to butyl acetate.

In the Ugelstad polymerization process the initial substantially monodisperse seed polymer particles may conveniently be produced by emulsion polymerization. We

- 7 -

have found that particularly suitable initial seed particles may be produced by effecting that emulsion polymerization under substantially oxygen-free conditions. Thus viewed from a further aspect the invention provides a process for the preparation of monodisperse polymer particles which comprises:

5 1) preparing monodisperse swellable seed particles by emulsion polymerization under substantially oxygen-free conditions;

10 2) where said seed particles are non-oligomeric (and optionally where they are oligomeric), (a) contacting said seed particles with an aqueous dispersion comprising an organic compound (e.g. a polymerization initiator) with a molecular weight below 5000 Dalton and a water solubility at 25°C of less than 15  $10^{-2}$ g/L, an anionic surfactant and, optionally an organic solvent in which said organic compound is soluble, and (b) allowing said organic compound to diffuse into said seed particles;

20 3) contacting the aqueous dispersion of seed particles with a monomer which, where said organic compound is used, is at least ten times more water soluble than said organic compound and allowing said monomer to diffuse into said seed particles to form an aqueous dispersion of swollen seed particles, and if required adding a water-soluble steric stabilizer, if required adding a porogen, and if required adding a polymerization initiator; and

25 4) initiating polymerization of said monomer in an aqueous dispersion containing a steric stabilizer in the continuous phase.

30 If desired the resulting particles may be further swollen and polymerized to obtain larger monodisperse polymer or oligomer particles. Where any of these 35 stages produces swollen particles having sizes from 1 to 25 $\mu$ m polyvinylpyrrolidone is preferably used as the steric stabilizer and if it produces swollen particles

- 8 -

having sizes above 15 $\mu\text{m}$  a cellulose ether is preferably used as the steric stabilizer. A cellulose ether may also be used as steric stabilizer where the mode diameter of said swollen particles is from 5 to 15  $\mu\text{m}$ .

5 Where the swollen particles have particle sizes below 5 $\mu\text{m}$ , and especially below 2 $\mu\text{m}$ , and especially where the organic compound used is a polymerization initiator, it is convenient to use as the surfactant a C<sub>8-16</sub> alkyl sulphate or sulphonate, especially a dodecyl sulphate, 10 e.g. sodium dodecyl sulphate, as this serves as both stabilizer and initiator uptake promoter. Where the seed particles have mode particle diameters below 1 $\mu\text{m}$ , the surfactant is especially preferably sodium dodecyl sulphate.

15 Where the monomer is an amino-functionalized monomer (or where two or more monomers are used and one comonomer is an amino functionalized monomer), it is preferred to add the initiator after the seed particles have been swollen and thus to use as the organic 20 compound (ie. substance I of EP-B-3905) a non-initiator, e.g. a material such as dioctyladipate. For such amino monomers, the initiator is preferably an azo compound, e.g. 2,2'-azobis-(2-methylbutyronitrile) or azo-bis-25 dimethylvaleronitrile. For other monomers, especially vinyl monomers (e.g. styrene) and acrylic monomers, it is preferred to use a peroxide initiator (e.g. dibenzoyl peroxide, lauroyl peroxide, t-butyl-peroxybenzoate, t-butyl-peroxypivalate and, especially, dioctanoyl peroxide) and to use the initiator as the organic 30 compound which promotes swelling of the seed particles.

Generally, it is preferred to use polymerization initiators that are activated by heat. In this way the initiator and monomer may be brought together within the swollen seed particles at a temperature below that of 35 which polymerization occurs and the aqueous dispersion may then be heated to the temperature at which polymerization is to take place, e.g. 50 to 90°C, more

- 9 -

generally 60 to 85°C. During the polymerization, the aqueous dispersion goes through a sticky state and the dispersion should be stirred as gently as possible while still sufficient to maintain a homogeneous dispersion.

5 In the final swelling and polymerization stage, it is preferred to raise the temperature, e.g. to 70 to 95°C, at the end of the polymerization stage so as to reduce the quantity of residual monomer.

10 Following preparation of the monodisperse polymer particles of the desired size (which may require two or more swelling and polymerization cycles, e.g. up to 10 such cycles), the polymer particles' surfaces may be derivatised as desired, e.g. by reaction with bifunctional reagents (e.g. diamines) which react with 15 functional groups present in monomers used in the final polymerization stage and serve to introduce the desired functional groups, e.g. amine, carboxyl, epoxy, hydroxyl, etc. Such functional groups may likewise be introduced by the use of a functionalised monomer or 20 comonomer, e.g. glycidyl methacrylate, HEMA, MMA or aminostyrene. Such groups are advantageous as the resultant particles are particularly suitable for end uses in applications such as combinatorial chemistry, peptide synthesis, supported catalysts and 25 chromatographic separation.

Depending on their desired end use, the monodisperse polymer particles may be coated (e.g. with metallic coatings); they may have materials, e.g. 30 magnetic crystals, specific binding partners (e.g. antibodies, avidin or streptavidin, etc.), or catalysts bound to their surface or deposited in pores or on the surface; or they may be expanded (e.g. using blowing agents).

The swelling and polymerization stages are 35 performed in aqueous dispersion in the presence of materials, e.g. surfactants, stabilizers, organic solvents, etc., which it is desirable to remove from the

- 10 -

particles. Likewise, where the polymerization produces a cross-linked polymer it may be desirable to remove linear polymers or oligomers which formed the seed particles, for example to avoid leakage during use in chromatography. Generally a water-miscible organic solvent in which the cross-linked polymer is insoluble, or an aqueous solution of such a solvent, may be used for this. However it is particularly suitable to use butyl acetate in this regard in view of its surprising effectiveness in removing undesired residues from the Ugelstad polymerization process. This use forms a further aspect of the present invention. Viewed from this aspect the invention provides a method of cleaning monodisperse polymer particles, in particular particles produced by swelling a seed polymer or oligomer particle in aqueous dispersion and polymerizing a monomer within the swollen seed particles, which method comprises contacting said monodisperse polymer particles with butyl acetate, e.g. by washing or rinsing with butyl acetate or a solution thereof.

The initial polymer seed (i.e. the particles not produced by the Ugelstad swelling and polymerization technique) is preferably prepared by dispersion or emulsion polymerization, in the latter case especially preferably under substantially oxygen-free conditions (e.g. under an inert gas atmosphere, for example a noble gas such as argon, helium, etc.), and with an oxygen content in the aqueous phase of between 0 and 5 ppm, more especially between 0 and 3 ppm, preferably between 0 and 2 ppm, particularly between 0.01 and 2 ppm. This can be achieved by boiling the water before use or, more preferably by purging liquid reagents with nitrogen. When purging liquid reagents with nitrogen, the length of time required depends upon the volume to be purged. For example, when purging a 2 litre vessel, a purging time of between 1 to 50 minutes is preferred, especially preferably purging for at least 10 minutes.

- 11 -

The aqueous phase in the emulsion polymerization contains an anionic surfactant stabilizer, e.g. an C<sub>8-16</sub> alkyl sulphate such as a decylsulphate, e.g. sodium decylsulphate. This is preferably present at a 5 concentration below its critical micelle concentration.

The unswollen initial seed preferably has a mode particle diameter in the range 0.2 to 1 $\mu$ m, especially 0.3 to 0.7 $\mu$ m, more especially 0.4 to 0.6 $\mu$ m. This can be achieved by mixing monomer, water and surfactant, 10 heating (e.g. to 80°C) and charging with initiator under vigorous stirring. The initial seeds produced by emulsion polymerization are preferably styrene polymers. Subsequent seeds may conveniently be polymeric or oligomeric.

15 In the process steps recited above for the processes of the invention, where the polymerization initiator is used as the organic compound (i.e. as substance I of the process of EP-B-3905) it is preferably an organic peroxide, e.g. tert-butyl 20 peroxyneodecanoate or more especially dioctanoyl peroxide (DOP) and it is preferably formed into a fine emulsion using water, the anionic surfactant (preferably sodium dodecyl sulphate or a sulfonate) and an organic solvent, e.g. acetone. The monomer may be but 25 preferably is not used as a solvent for the peroxide initiator; if it is used as a solvent it is preferred that only a relatively small amount of the monomer be used.

30 In general, emulsification is preferably effected using a high pressure mixer (e.g. a pressure homogenizer), or a rotor stator mixer, to give a mode droplet diameter in the range 0.05 to 5 $\mu$ m, more preferably 0.05 to 0.5 $\mu$ m, especially 0.05 to 0.3 $\mu$ m. During emulsifications, the surfactant is preferably 35 present above its critical micelle concentration, e.g. at a concentration of 3 to 10 g/L, more preferably 4 to 6 g/L (the critical micelle concentration for sodium

- 12 -

dodecyl sulphate is about 2.5 g/L). However during polymerization stages, the surfactant is preferably present below its critical micelle concentration, e.g. at less than 1.5 g/L, conveniently 0.1 to 1.0 g/L. This 5 can be achieved either by dilution, for example, with water after emulsion formation but before polymerization initiation. Alternatively, the desired concentration may be achieved by dilution, for example with water or a solution of a steric stabilizer after emulsion formation 10 but before polymerization initiation. As a further alternative, the desired concentration may be realised by adding an appropriately diluted solution of steric stabilizer prior to emulsion formation.

During the uptake of the organic compound by the 15 polymer seed particles, the temperature of the dispersion is preferably maintained between 20 and 50°C as precipitation may occur at lower temperatures and new particles may form at higher temperatures. Generally temperatures of 25°C ± 2°C are preferred.

20 During this uptake phase the dispersion is preferably stirred. The time required for uptake is dependant on the seed diameter, the quantity and nature of the organic compound, the emulsion droplet size and the quantity and nature of surfactant and organic 25 solvent. Generally a period of 1 to 5 days, more particularly 2 to 3 days, will be sufficient. Where the organic compound is an initiator it is important that uptake be at least substantially complete so as to avoid out-of-size particles.

30 The organic solvent concentration in the dispersion during organic compound uptake is conveniently 5 to 15% w/w.

The monomers and comonomers used in the process of 35 the invention are preferably vinyl monomers (e.g. styrene), acrylic monomers and methacrylate monomers and monomers copolymerizable therewith, e.g. styrene, divinylbenzene (DVB), ethyl vinyl benzene, vinyl

- 13 -

pyridine, amino-styrene, methyl-styrene, ethylene  
dimethacrylate, (EDMA), hydroxyethylmethacrylate (HEMA),  
methyl methacrylate (MMA), glycidyl methacrylate (GMA),  
vinyl benzyl chloride (VBC), vinylchloride (VC),  
5 dimethyl styrene, ethyl styrene, ethyl-methyl-styrene,  
p-chlorostyrene, 2,4-dichlorostyrene, acrylic acid,  
methyl acrylate, ethyl acrylate, butylacrylate,  
methacrylic acid, ethyl methylmethacrylate, maleic acid,  
maleic anhydride, dimethyl maleate, diethyl maleate,  
10 dibutyl maleate, fumaric acid, dimethyl fumarate,  
diethyl fumarate and acrylonitrile.

In the process of the invention the initial polymer  
seed, e.g. made by emulsion polymerization, is a  
polymer. Especially preferably, the initial polymer  
15 seed is a styrene homo or copolymer, e.g. a styrene  
homopolymer or a styrene-divinyl benzene copolymer.  
Most preferably, initial seeds prepared by emulsion  
polymerization will be homopolymers, especially  
polystyrene. Initial seeds prepared by other  
20 techniques, e.g. dispersion polymerization may be  
homopolymers or copolymers, and may be oligomeric or  
polymeric. Such seeds typically may be 1 to 10  $\mu\text{m}$  in  
mode diameter and optionally may contain some cross-  
linker. Initial seeds used in this invention which are  
25 produced by emulsion polymerization, on the other hand,  
are typically of less than or equal to about 1  $\mu\text{m}$  in  
diameter.

Intermediate seeds may be either polymer or  
oligomer seeds. Throughout this application, oligomer  
30 is intended to refer to polymers having low weight  
average molecular weight (for example up to 5000  
Daltons, e.g. 1000 to 4000 D, especially 1500 to 3000  
D), corresponding for example up to 50, more  
particularly 10 to 25 monomer units. Oligomer seeds  
35 have the advantage that their swelling capacity is  
generally much greater than that of the longer chain  
polymers.

For intermediate or larger sized seeds, e.g. having a mode particle diameter of about 1 $\mu$ m or above before swelling, it may be desirable to incorporate a chain transfer agent, e.g. a halogenated alkane as described by Ugelstad in US-A-4186120. This has the advantage of producing a polymer with a bimodal molecular weight distribution in the polymerization stage. The lower molecular weight component results in the particles produced in that polymerization stage having a greater swelling capacity for subsequent swelling and polymerization stages.

As an alternative to the use of a chain transfer agent, a high initiator concentration may be used in oligomer production. In this regard, the techniques of US-A-4530956 (Ugelstad), the disclosure of which is incorporated by reference, may be used.

It is also preferred to include a water-soluble polymerization inhibitor (e.g. potassium iodide) in the aqueous phase to prevent nucleation of particles.

Where a porous product is desired, then a porogen should be incorporated in the swollen seed particles, preferably in at least the final swelling and polymerization stage. As porogens can be used organic substances which are not polymerized in the polymerization stage and which can be removed from the particles after polymerization thereby producing porous particles. Porogens can also be used as blowing agents - particles impregnated with such materials, on heating may expand as the porogen vaporizes. Examples of suitable porogens include organic acids, alcohols, esters, aromatic solvents, optionally substituted aliphatic hydrocarbons having up to 12 carbons, e.g. toluene, cyclohexanol, butyl acetate, propane, pentane, cyclopentane, cyclobutane, heptane, methyl chloride, ethyl chloride, dichlorodifluoromethane, etc. Toluene and n-heptane are preferred, especially in a volume ratio of 1:10 to 10:1, more particularly 1:4 to 4:1.

- 15 -

The porogen is conveniently introduced in admixture with the monomer.

By the use of a combination of porogens, at least one of which is a solvent for the polymer produced in the polymerization stage and at least one of which is a not a solvent for that polymer, it is possible to achieve a desired pore size distribution in the resulting porous particles. Thus for example for vinyl polymers (e.g. styrene) toluene can be used as a solvent porogen and n-heptane as a non-solvent porogen. The use of the term "solvent" in this specific context is not intended to convey that the swollen particles are capable of dissolving fully in this solvent, or that the swollen particles are incapable of dissolving to any extent whatsoever in the non-solvent porogen. Thus the combination of the two types of porogen enables the desired pore size distribution in the resulting porous particles to be achieved. This use of a porogen combination forms a further aspect of the invention.

Viewed from this aspect the invention provides a process for the preparation of porous monodisperse polymer particles which process comprises:

1) either

(a) forming an aqueous dispersion comprising (i) monodisperse swellable seed polymer (or oligomer) particles, (ii) droplets comprising an organic compound (e.g. a polymerization initiator) with a molecular weight below 5000 Dalton and a water solubility at 25°C of less than 10<sup>-2</sup>g/L, (iii) an anionic surfactant, and, optionally, (iv) an organic solvent in which said organic compound is soluble;

and (b) allowing said organic compound to diffuse into said seed particles,

or

- 16 -

(a) forming an aqueous dispersion comprising monodisperse swellable seed oligomer particles and preferably an anionic surfactant;

5 2) contacting the aqueous dispersion of seed particles with a monomer which, where said organic compound is present, is at least ten times more water soluble than said organic compound, and allowing said monomer to diffuse into said seed particles to form an aqueous dispersion of swollen seed particles and if required adding a water-soluble steric stabilizer, if required adding a porogen, and if required adding a polymerization initiator; and

10 15 3) initiating polymerization of said monomer in an aqueous dispersion of swollen seed particles, characterised in that said swollen seed particles contain at least two porogens, at least one of which is a solvent for the polymer produced in step (3) and at least one of which is not a solvent for the polymer produced in step (3).

20 In this aspect, the ratio with regard to increase in diameter is preferably greater than or equal to 4.5.

25 In general, a cross-linking monomer (such as divinylbenzene) can be used as 0 to 100% w/w of the monomer diffused into the seeds, for example as at least 30% for the production of porous particles and up to 0.5% for the production of very highly swellable particles.

30 35 In the preparation of porous particles and many other particles, it is necessary to include a crosslinking agent or alternatively to use as a monomer or comonomer a compound with more than one polymerization site, e.g. a compound with more than one polymerizable carbon-carbon double bond, for example a diene such as divinyl benzene, or compounds such as hexanediol dimethacrylate, trimethylol propane trimethacrylate and divinyl benzyl ether. Particularly desirably the monodisperse polymer particles produced

- 17 -

according to the invention are 30 to 100% divinyl benzene, more especially 60 to 95%, particularly 70 to 90%, more particularly 75 to 82% (where the percentages are by weight of divinylbenzene monomer residue relative to the total monomer residue).

It has been found that the Ugelstad processes can be used particularly effectively to produce functionalized or functionalizable monodisperse particles where the monomer dispersed into the seeds in at least one swelling stage, preferably the final stage, comprises at least two acrylic or methacrylic acid or ester monomers, more preferably at least one being glycidyl methacrylate. Viewed from a further aspect therefore the invention provides a process for the preparation of monodisperse polymer particles which process comprises:

1) either

(a) forming an aqueous dispersion comprising (i) monodisperse swellable seed polymer (or oligomer) particles, (ii) droplets comprising an organic compound (e.g. a polymerization initiator) with a molecular weight below 5000 Dalton and a water solubility at 25°C of less than  $10^{-2}$ g/L, (iii) an anionic surfactant, and, optionally, (iv) an organic solvent in which said organic compound is soluble;

and (b) allowing said organic compound to diffuse into said seed particles;

or

(a) forming an aqueous dispersion comprising monodisperse swellable seed oligomer particles and preferably an anionic surfactant;

2) contacting the aqueous dispersion of seed particles with a monomer which, where said organic compound is present, is at least ten times more water soluble than said organic compound, and allowing said monomer to diffuse into said seed particles to form an aqueous dispersion of swollen seed particles and if

- 18 -

required adding a water-soluble steric stabilizer, if required adding a porogen, and if required adding a polymerization initiator; and

5 3) initiating polymerization of said monomer in an aqueous dispersion of swollen seed particles, characterised in that said monomer comprises at least two acrylic or methacrylic acid or ester monomers, more preferably at least one being glycidyl methacrylate.

10 In this aspect, the ratio with regard to increase in diameter is preferably greater than or equal to 4.5.

Coefficient of variation (CV) is determined in percentage as

$$CV = \frac{100 \times \text{standard deviation}}{\text{mean}}$$

15

where mean is the mean particle diameter and standard deviation is the standard deviation in particle size. CV is preferably calculated on the main mode, ie. by 20 fitting a monomodal distribution curve to the detected particle size distribution. Thus some particles below or above mode size may be discounted in the calculation which may for example be based on about 90%, more usually about 99% of total particle number (of 25 detectable particles that is). Such a determination of CV is performable on a Coulter Counter Channelizer 256 particle size analyser.

30 Embodiments of the invention are illustrated further by the following non-limiting Examples:

**EXAMPLE 1**

Porous crosslinked polystyrene particles, 30 $\mu$ m

35 1400g of water, 84g of dioctanoyl peroxide (DOP), 140g of acetone and 7g of sodium dodecyl sulphate (SDS) were homogenized in a two stage Manton Gaulin homogenizer with 380kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the

- 19 -

second stage for 8-9 min.

After homogenization 178.1g of the emulsion were charged with a seed suspension of monodisperse oligomeric 5 styrene particles having a particle diameter of 5 $\mu$ m. There were used 21.9g of seed suspension containing 19.8g of water and 2.1g of oligomeric particles.

After stirring for 3 days at 25°C, 180.8g of the 10 activated seed particles were charged with an emulsion containing 1683g of water, 0.6g of sodium dodecyl sulfate (SDS), 2.6g of Methocel K100 (HPMC=Hydroxy Propyl Methyl Cellulose), 117g of 80% divinylbenzene (DVB) [ie. 80% by weight DVB, 20% by weight ethyl vinyl 15 benzene and other byproducts of DVB production], 223g of porogen (toluene:n-heptane in a 1:2 volume ratio). The emulsion was homogenized at 330kg/cm<sup>2</sup> in the first stage and 50kg/cm<sup>2</sup> in the second stage for 6-7 min.

20 After swelling for 15 hrs at 25°C, 5.3g of methocel K100 dissolved in 788g of water were charged to the reactor. The dispersion was then polymerized for 10 hrs at 70°C. A monodisperse suspension was formed having a particle diameter of 30 $\mu$ m.

25 The particles were separated from the liquid phase by flotation and the liquid phase was discharged. The particles were then cleaned with 2 litres of methanol by stirring for 1 hour followed by sedimentation. After 30 sedimentation the liquid phase was discharged, new methanol (2 litres) was charged and the described procedure was repeated 4 times. The particle suspension was then sieved through a 100 $\mu$ m sieving cloth. Then the particle suspension was diafiltered with 6 litres of butylacetate followed by 6.7 litres of methanol. Finally the particles were cleaned by sedimentation and discharging of the liquid phase, with 2 litres of

- 20 -

methanol minimum 3 times.

The final product was 30 $\mu$ m polymer particles in a clear liquid phase without impurities.

5

**EXAMPLE 2**

**Porous acrylic particles, 30 $\mu$ m**

10 1400g of water, 84g of DOP, 140g of acetone and 7g of SDS were homogenized in a two stage Manton Gaulin homogenizer with 380kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 8-9 min.

15 After homogenization, 88.4g of the emulsion were charged with a seed suspension of monodisperse oligomeric styrene particles having a particle diameter of 5 $\mu$ m. There were used 9.6g of seed suspension containing 8.75g of water and 0.85g of oligomeric particles.

20 After stirring for 3 days at 25°C, 89g of the activated seed particles were charged with an emulsion containing 844g of water, 1.3g of Methocel K100, 44.9g of ethylene dimethylacrylate (EDMA), 11.4g of hydroxy ethyl methacrylate (HEMA), 113g of porogen (cyclohexanol: butylacetate in a 1:1 volume ratio). The mixture was 25 emulsified with a Ultra Turrax at maximum speed for 10 min.

30 After swelling for 2 hrs at 25°C, 0.4g of potassium iodide (KI) dissolved in 395g of water were charged to the reactor and the dispersion was then polymerized for 1 hr at 50°C, 3 hrs at 60°C and 1 hr at 70°C. A monodisperse suspension was formed having a particle diameter of 30 $\mu$ m.

35

**EXAMPLE 3**

**Solid polystyrene particles, 20 $\mu$ m**

- 21 -

1400g of water, 84g of DOP, 140g of acetone and 7g of SDS were homogenized in a two stage Manton Gaulin homogenizer with 380kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 8-9 min.

5

After homogenization 159g of the emulsion were charged with a seed suspension of monodisperse oligomeric styrene particles having a particle diameter of 5μm. There were used 43.9g of seed suspension containing 10 39.7g of water and 4.2g of oligomeric particles.

15 After stirring for 2 days at 25°C, 184.4g of the activated seed particles were charged with an emulsion containing 836g of water, 1.5g of Methocel K100, 348.8g styrene. The emulsion was homogenized at 400kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 4-5 min.

20 After swelling for 2 hrs at 25°C, 3g of Methocel K100 dissolved in 427g of water were charged to the reactor and then the dispersion was polymerized for 1 hr at 60°C and 9 hrs at 70°C. A monodisperse suspension was formed having a particle diameter of 20μm.

25

#### EXAMPLE 4

#### Solid crosslinked polystyrene particles, 54μm

30

1400g of water, 42g of DOP, 222g of acetone and 7g of SDS were homogenized in a two stage Manton Gaulin homogenizer with 400kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 8-9 min.

35

After homogenization 159g of the emulsion were charged with a seed suspension of monodisperse oligomeric styrene particles having a particle diameter of 9.5μm. There were used 17.6g of the seed suspension containing 16.6g of water and 1g of oligomeric particles.

- 22 -

5 After stirring for 3 days at 25°C, 146.3g of the activated seed particles were charged with an emulsion containing 1198g of water, 2.5g of Methocel K100, 228g styrene, 7.3g 65% DVB. The emulsion was homogenized at 400kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 5-6 min.

10 After swelling for 1 hour at 25°C, 0.5g of Methocel K100 and 0.5g KI dissolved in 500g of water were charged to the reactor and then the dispersion was polymerized for 1 hr at 60°C and 9 hrs at 70°C. A monodisperse particle suspension was formed having a particle diameter of 54μm.

15

**EXAMPLE 5**

**Solid crosslinked polystyrene particles, 15μm**

20 1400g of water, 84g of DOP, 140g of acetone and 7g of SDS were homogenized in a two stage Manton Gaulin homogenizer with 400kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 8-9 min.

25 After homogenization 75.8g of the emulsion were charged with a seed suspension of monodisperse oligomeric styrene particles having a particle diameter of 3.2μm. There were used 22g of the seed suspension containing 20g of water and 2g of oligomeric particles.

30 35 After stirring for 1 day at 25°C, 85g of the activated seed particles were charged with an emulsion containing 784g of water, 1.25g of SDS, 204.3g styrene, 0.37g of 80% DVB. The emulsion was homogenized at 400kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 4-5 min.

After swelling for 5 hrs at 25°C, 15g of PVP K90 (Poly Vinyl Pyrrolidone) and 0.4g of potassium iodide dissolved

- 23 -

in 702g of water were charged to the reactor and then the dispersion was polymerized for 1 hr at 60°C and 9 hrs at 70°C. A monodisperse suspension was formed having a particle diameter of 15 $\mu$ m.

5

**EXAMPLE 6**

**Porous crosslinked polystyrene particles, 4.5 $\mu$ m**

10 4970g of water, 248.5g of DOP and 24.85g of SDS were homogenized in a two stage Manton Gaulin homogenizer with 400kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 25 min.

15 After homogenization 3947.6g of the emulsion were charged with a seed suspension of monodisperse oligomeric styrene particles having a particle diameter of 1 $\mu$ m. There were used 1691.2g of the seed suspension containing 1555.2g of water and 136.0g of oligomeric particles.

20

After stirring for 20 hrs at 25°C, 5126.2g of the activated seed particles were charged with an emulsion containing 42576g of water, 26.47g of SDS, 536.5g of PVP K-30, 2989.7g of 62.5% DVB, 1991.7g of styrene and 25 4727.0g of porogen (toluene). The emulsion was homogenized at 380kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 30 min.

30 After swelling for 20 hrs at 25°C, 42026.4g of water were charged to the reactor and then the dispersion was polymerized for 1 hr at 60°C, 4 hrs at 70°C and 2.5 hrs at 80°C. A monodisperse suspension was formed having a particle diameter of 4.5 $\mu$ m.

35

**EXAMPLE 7**

**Porous crosslinked polystyrene particles, 2.8 $\mu$ m**

- 24 -

2630g of water, 214.4g of DOP, 291.9g of acetone and 14.73g of SDS were homogenized in a two stage Manton Gaulin homogenizer with 400kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 25 min.

5

After homogenization 2994.6g of the emulsion were charged with a seed suspension of monodisperse polystyrene particles having a particle diameter of 0.5μm. There were used 341.3g of seed suspension containing 290.4g of water and 50.9g of polymeric particles.

10

After stirring for 20 hrs at 25°C, 3032.6g of the activated seed particle suspension were charged with an emulsion containing 43375.1g of water, 31.42g of SDS, 1412.7g of PVP K-30, 2989.6g of 62.9% DVB, 1998.2g of styrene and 4780.7g of porogen (toluene). The emulsion was homogenized at 380kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 60 min.

15

After swelling for 20 hrs at 25°C, 42379.7g of water were charged to the reactor and then the dispersion was polymerized for 1 hr at 60°C, 4 hrs at 70°C and 2.5 hrs at 80°C. A monodisperse suspension was formed having a particle diameter of 2.8μm.

20

25

#### **EXAMPLE 8**

#### **Porous crosslinked polystyrene particles, 2.6μm**

30

1548g of water, 16g of PVP-K30, 2.4g SDS, 176.6g of 63% DVB, 44g of styrene, 204.6g of porogen (toluene) and 5.6g of 2,2'-azobis(2-methylbutyronitrile) (AMBN) were homogenized in a two stage Manton Gaulin homogenizer with 400kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 35 min.

35

After homogenization 1013.4g of the emulsion were

- 25 -

charged with a seed suspension of monodisperse oligomeric styrene particles having a particle diameter of 0.65 $\mu$ m. There were used 40.4g of seed suspension containing 36.8g of water and 3.58g of oligomeric particles.

5

After swelling for 20 hrs at 25°C, 8g PVP K-30, and 0.8g of potassium iodide dissolved in 794g of water were charged to the reactor and then the dispersion was 10 polymerized for 1 hr at 60°C, 4 hrs at 70°C and 2.5 hrs at 80°C. A monodisperse suspension was formed having a particle diameter of 2.6 $\mu$ m.

10

**EXAMPLE 9**

15 **Preparation of initial seed particles, 0.5 $\mu$ m**

280g styrene was extracted with 500ml 10 wt.% sodium hydroxide and then washed with water to pH7 and then flushed with argon for 10 min. In a 2L reactor 1400g of 20 water and 0.53g of borax were heated to 80°C, and 100g water was evaporated off to remove oxygen. Then 0.56g sodium decyl sulphate in 50ml boiled water was charged and stirred for 10 min, then the washed and substantially oxygen free styrene was charged and 25 stirred for 15 min. Then 0.84g potassium peroxodisulphate was charged in 100ml boiled water. The mixture was kept at 80°C in an argon atmosphere for 13 hours. A monodisperse suspension of polymeric particles was formed having a particle diameter of 0.5 $\mu$ m.

30

**EXAMPLE 10**

**Solid methacrylic particles with amine groups, 6 $\mu$ m**

35 900g of water, 90g of DOP; 90g of acetone and 5.4g of SDS were homogenized in a two stage Manton Gaulin homogenizer with 380kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 6-7 min.

- 26 -

After homogenization 77.0g of the emulsion were charged with a seed suspension of monodisperse oligomeric styrene particles having a particle diameter of 1 $\mu$ m. There were used 14.5g of seed suspension containing 5 13.2g of water and 1.3g of oligomeric particles.

After stirring for 1 day at 25°C, 83.3g of the activated seed particles were charged with 864.6g of water, 2.0g of SDS, 158.9g of methyl methacrylate (MMA), 45.4g 10 glycidyl methacrylate (GMA) and 22.7g ethylene glycol-dimethacrylate, (EDMA) .

After swelling for 15 hrs at 25°C, 788g of water were charged to the reactor and then the dispersion was 15 polymerized for 6 hrs at 70°C. Then 38.4g ethylenediamine were charged to the reactor and then reaction was allowed to proceed for 18 hrs. A monodisperse suspension was formed having a particle diameter of 6 $\mu$ m.

20

**EXAMPLE 11**

**Core and shell particles, 10 $\mu$ m**

Step 1

25 1200g of water, 120g of DOP, 240g of acetone and 7.2g of SDS were homogenized in a two stage Manton Gaulin homogenizer with 400kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 7-8 min.

30 After homogenization 83g of the emulsion were charged with a seed suspension of monodisperse polystyrene particles having a particle diameter of 2 $\mu$ m. There were used 7.9g of the seed suspension containing 6.5g of water and 1.4g of polymeric particles.

35

After stirring for 1 day at 25°C, acetone was removed by evaporation under vacuum and 71g of the activated seed

- 27 -

particles were charged with 907g of water, 2.1g of SDS, 138.4g of methylstyrene, 34.6g of 55% DVB.

5 After swelling for 20 hrs at 25°C, 0.4g of KI dissolved in 647g of water were charged to the reactor and then polymerized for 5 hrs at 70°C (core). Then the batch was cooled down to 25°C.

Step 2

10 550g of the suspension of step 1 was taken and the aqueous was charged with 0.1g of Methocel J 75MS (Hydroxy Propyl Methyl Cellulose), 0.05g of KI and 0.1g of SDS dissolved in 230g of water. To this batch was added a mixture of 15.6g MMA, 12.5g of GMA and 3.1g of 15 EDMA.

20 After stirring for 2 hrs at 25°C, the temperature was raised to 65°C for 1 hr and further to 70°C for 5 hrs. The final mixture was monodisperse and contained particles having a diameter of about 10 $\mu$ m.

**EXAMPLE 12**

**Solid polystyrene particles with chlorine groups, 200 $\mu$ m**

25 1370g of water, 82g of DOP, 205g of acetone and 8.2g of SDS were homogenized in a two stage Manton Gaulin homogenizer with 400kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 8-9 min.

30 After homogenization, 166g of the emulsion were charged with a seed suspension of monodisperse oligomeric styrene particles having a particle diameter of 71 $\mu$ m. There were used 79g of the seed suspension containing 71.2g of water and 7.8g of oligomeric particles.

35 After stirring for 2 days at 25°C, 222g of the activated seed particles were charged with an emulsion containing

- 28 -

1583g of water, 8.5g of Methocel K100, 124.4g styrene, 3g of 62.8% DVB, 58.5g of Vinyl Benzyl Chloride (VBC). The emulsion was homogenized at 400kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 5-6 min.

5

After swelling for 1 hr at 25°C, the temperature was raised to 60°C for 1 hr and further to 70°C for 10 hrs. A monodisperse suspension was formed having a particle diameter of 200μm.

10

**EXAMPLE 13**

**Porous crosslinked polystyrene particles containing amine functionality, 30μm**

15

1500g of water, 119g of bis(2-ethylhexyl)adipate, 152g of acetone and 8g of sodium dodecyl sulphate (SDS) were homogenized in a two stage Manton Gaulin homogenizer at 400kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 8-9 min.

20

After homogenization, 499g of the emulsion was charged with a seed suspension of monodisperse oligomeric styrene particles having a particle diameter of 5μm. 93g of a seed suspension containing 8g of oligomeric particles and 85g of water was used.

25

After stirring at 45°C for 1 day, 96.9g of the seed suspension containing activated seed particles were charged to 1097.7g of an emulsion containing 798.3g of water, 1.2g of Methocel K-100, 0.3g of sodium dodecyl sulphate 34.74g of 80% divinylbenzene (DVB) [i.e. 80% by weight DVB, 20% by weight ethyl vinyl benzene and other byproducts in DVB production], 52.8g of styrene, 4.2g of 2,2'-azobis(2-methylbutyronitrile) and 205.7g of toluene. The emulsion was homogenized at 400kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 8-9 min.

30

35

- 29 -

After swelling at 25°C for 0.5 hours, a mixture of 299.8g of water, 0.5g of Methocel K-100, 0.1g of sodium dodecyl sulphate and 5.1g of 4-amino-styrene was charged and the swelling continued for additional 3 hours.

5 506.2g of water and 3.37g of Methocel K-100 were then charged to the reactor. The dispersion was then polymerized for 1 hour at 60°C and 17 hours at 70°C, yielding a suspension of particles having a diameter of 30 $\mu$ m.

10 The particles were cleaned as described in Example 1.

**EXAMPLE 14**

15 **Porous crosslinked polystyrene particles containing amine functionality, 30 $\mu$ m**

850g of water, 110.50g of bis(2-ethylhexyl)adipate, 141.95g of acetone and 4.25g of sodium dodecyl sulphate (SDS) were homogenized in a two stage Manton Gaulin 20 homogenizer at 400kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 8-9 min.

25 After homogenization, 102.68g of the emulsion was charged with a seed suspension of monodisperse oligomeric styrene particles having a particle diameter of 5 $\mu$ m. 27.21g of seed suspension containing 1.71g of oligomeric particles and 26.2g of water was used.

30 After stirring at 45°C for 24 hours, 87.06g of the seed suspension containing activated seed particles were charged to 1436.08g of an emulsion containing 1035.84g of water, 1.58g of Methocel K-100, 0.5g of sodium dodecyl sulphate, 53.41g of 80% divinylbenzene (DVB) [i.e. 80% by weight DVB, 20% by weight ethyl vinyl 35 benzene and other byproducts in DVB production], 56.07g of styrene, 6.71g of 2,2'-azobis(2-methylbutyronitrile), 269.41g of toluene and 12.56g of 4-amino-styrene. The

- 30 -

emulsion was homogenized without addition of 4-amino-styrene at 400kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 8-9 min before the emulsion was mixed with 4-amino-styrene.

5

After swelling at 27°C for 1 hour, a mixture of 473.69g of water and 3.16g of Methocel K-100 was then charged to the reactor. The dispersion was then polymerized for 1 hour at 60°C and 10 hours at 70°C, yielding a suspension 10 of particles having a diameter of 30μm.

The particles were cleaned as described in Example 1.

#### EXAMPLE 15

15 Crosslinked polystyrene particles containing amine functionality, 32 μm

20 1380g of water, 179g of bis(2-ethylhexyl)adipate, 230g of acetone and 7g of sodium dodecyl sulphate (SDS) were homogenized in a two stage Manton Gaulin homogenizer at 400 kg/cm<sup>3</sup> in the first stage and 100 kg/cm<sup>3</sup> in the second stage for 10-12 minutes.

25 After homogenization 292g of the emulsion was charged with a seed suspension of monodisperse oligomeric styrene particles having a particle diameter of 5 μm. 79g of seed suspension containing 7g of oligomeric particles and 72g of water was used.

30 35 After stirring at 45°C for 1 day, 52.5g of the seed suspension containing activated seed particles were charged to 850.5g of an emulsion containing 0.9g of Methocel K-100, 0.3g of sodium dodecyl sulphate (SDS), 2.1g of divinylbenzene (DVB) [i.e. 80% by weight DVB, 20% by weight ethyl vinyl benzene and other byproducts in DVB production], 174.1g of styrene, 58.7g of amino styrene, and 12.9g of 2,2'-azobis(2-methylbutyro-

- 31 -

nitrile). The mixture was emulsified for 10 minutes by using an Ultra Turax mixer.

5 After swelling at 27°C for 1 hour, 281.6g of water and 1.9g of Methocel K-100 were charged to the reactor. The dispersion was then polymerized for 1 hour at 60°C and 10 hours at 70°C, yielding a suspension of particles having diameter of 32  $\mu\text{m}$ .

10 The particles were cleaned as described in Example 1. Diameter was measured on particles dispersed in water, butylacetate and tetrahydrofuran respectively.

#### EXAMPLE 16

15 Crosslinked polystyrene particles containing amine functionality, 35  $\mu\text{m}$

20 1380g of water, 179g of bis(2-ethylhexyl)adipate, 230g of acetone and 7g of sodium dodecyl sulphate (SDS) were homogenized in a two stage Manton Gaulin homogenizer at 400 kg/cm<sup>3</sup> in the first stage and 100 kg/cm<sup>3</sup> in the second stage for 10-12 minutes.

25 After homogenization, 292g of the emulsion was charged with a seed suspension of monodisperse oligomeric styrene particles having a particle diameter of 5  $\mu\text{m}$ . 79g of seed suspension containing 7g of oligomeric particles and 72g of water was used.

30 35 After stirring at 45°C for 1 day, 52.2g of the seed suspension containing activated seed particles were charged to 850.5g of an emulsion containing 0.9g of Methocel K-100, 0.3g of sodium dodecyl sulphate (SDS), 5.9g of divinylbenzene (DVB) [i.e. 80% by weight DVB, 20% by weight ethyl vinyl benzene and other byproducts in DVB production], 166.0g of styrene, 63.0g of amino styrene and 12.9g of 2,2'-azobis(2-methylbutyro-

- 32 -

nitrile). The mixture was emulsified for 10 minutes by using an Ultra Turax mixer.

After swelling at 27°C for 1 hour, 281.6g of water and 5 1.9g of Methocel K-100 were charged to the reactor. The dispersion was then polymerized for 1 hour at 60°C and 10 hours at 70°C, yielding a suspension of particles having diameter of 35  $\mu\text{m}$ .

10 The particles were cleaned as described in Example 1. Diameter was measured on particles dispersed in water, butylacetate and tetrahydrofuran respectively.

**EXAMPLE 17**

15 **Crosslinked polystyrene particles containing amine functionality, 35  $\mu\text{m}$**

20 1380g of water, 179g of bis(2-ethylhexyl)adipate, 230g of acetone and 7g of sodium dodecyl sulphate (SDS) were homogenized in a two stage Manton Gaulin homogenizer at 400 kg/cm<sup>3</sup> in the first stage and 100 kg/cm<sup>3</sup> in the second stage for 10-12 minutes.

25 After homogenization, 292g of the emulsion was charged with a seed suspension of monodisperse oligomeric styrene particles having a particle diameter of 5  $\mu\text{m}$ . 79g of seed suspension containing 7g of oligomeric particles and 72g of water was used.

30 After stirring at 45°C for 1 day, 52.2g of the seed suspension containing activated seed particles were charged to 850.5g of an emulsion containing 0.9g of Methocel K-100, 0.3g of sodium dodecyl sulphate (SDS), 8.8g of divinylbenzene (DVB) [i.e. 80% by weight DVB, 35 20% by weight ethyl vinyl benzene and other byproducts in DVB production], 167.3g of styrene, 58.7g of amino styrene, and 12.9g of 2,2'-azobis(2-methylbutyro-

- 33 -

nitrile). The mixture was emulsified for 10 minutes by using an Ultra Turax mixer.

5 After swelling at 27°C for 1 hour, 281.6g of water and 1.9g of Methocel K-100 were charged to the reactor. The dispersion was then polymerized for 1 hour at 60°C and 10 hours at 70°C, yielding a suspension of particles having diameter of 35 µm.

10 The particles were cleaned as described in Example 1. Particle diameter was measured on particles dispersed in water, butyl acetate and tetrahydrofuran respectively.

15 Elemental analysis showed a content of 3.0 wt.% nitrogen and 0.38 wt.% oxygen.

**EXAMPLE 18**

**Further functionalisation of amine-functionalised particles with carboxyl and amide functionality**

20 5g of the particles produced in Example 17 in methanol were washed with dioxane (3 x 180 ml). 2.07g of succinic anhydride was added to the dioxane suspension (96g). The mixture was heated and mechanically stirred at 40°C for 3 hours. The particles were washed with dioxane (2 x 200 ml), methanol (100 ml) and dioxane (200 ml). Ir spectra showed a broad peak at 1750 to 1650 cm<sup>-1</sup> which indicates formation of both amide and carboxylic acid groups.

25 30 Elemental analysis of dried particles showed a content of 2.5 wt.% nitrogen and 9.3 wt.% oxygen. This indicates an amine conversion near 100%.

35 **EXAMPLE 19**

**Further functionalisation of amine-functionalised particles with amide functionality**

- 34 -

5g of the particles produced in Example 17 in methanol were washed with dioxane (3 x 180 ml). 4.23g of bromoacetic acid bromide and 3.0g diisopropylethylamine was added to the dioxane suspension (79g). The mixture 5 was mechanically stirred at 20°C for 1 hour. The particles were washed with dioxane (2 x 150 ml), dioxane with 20% water and 1g diisopropylethylamine (150 ml) and dioxane (2 x 150 ml).

10 Ir spectra showed a peak at 1685  $\text{cm}^{-1}$  which indicates formation of amide groups.

Elemental analysis of dried particles showed a content of 13.2 wt% bromine indicating a conversion of 96%.

15

**EXAMPLE 20**

**Porous crosslinked polystyrene particles, 5.0  $\mu\text{m}$**

20 2020.0g of water, 202.0g of DOP, 202.0g of acetone and 10.10g of SDS were homogenized in a two stage Manton Gaulin homogenizer with 400  $\text{kg}/\text{cm}^2$  in the first stage and 100  $\text{kg}/\text{cm}^2$  in the second stage for 10 minutes.

25 After homogenization, 1429.3 g of the emulsion were charged with a seed suspension of monodisperse oligomeric styrene particles having particle diameter of 0.9  $\mu\text{m}$ . There were used 372.8g of seed suspension containing 341.1g of water and 31.7g of oligomeric particles.

30

After stirring for 23 hours at 25°C, 581.3g of the activated seed suspension were charged with an emulsion containing 7053.9g of water, 18.0g of Methocel K-100, 883.0g of 80% divinylbenzene (DVB) [i.e. 80% by weight 35 DVB, 20% by weight ethyl vinyl benzene and other byproducts in DVB production], 168.1 g of toluene and 525.6g of n-heptane. The emulsion was homogenized in a

- 35 -

two stage Manton Gaulin homogenizer with 400 kg/cm<sup>2</sup> in the first stage and 100kg/cm<sup>2</sup> in the second stage for 30 minutes.

5 After swelling for 20 hrs at 25°C, 3234.2g of water and 35.9g of Methocel K-100 were charged to the reactor and then the dispersion was polymerized for 1 hour at 60°C and 10 hours at 70°C. A monodisperse suspension was formed having a particle diameter of 5  $\mu\text{m}$ .

10

The particles were cleaned as described in Example 1.

Claims:

1. A process for the preparation of monodisperse polymer particles which process comprises:

5 1) either

(a) forming an aqueous dispersion comprising (i) monodisperse swellable seed polymer (or oligomer) particles, (ii) droplets comprising an organic compound (e.g. a polymerization initiator) with a molecular weight below 5000 Dalton and a water solubility at 25°C 10 of less than 10<sup>-2</sup>g/L, (iii) an anionic surfactant, and, optionally, (iv) an organic solvent in which said organic compound is soluble;

15 and (b) allowing said organic compound to diffuse into said seed particles,

or

(a) forming an aqueous dispersion comprising monodisperse swellable seed oligomer particles and preferably an anionic surfactant;

20 2) contacting the aqueous dispersion of seed particles with a monomer which, where said organic compound is present, is at least ten times more water soluble than said organic compound, and if required a water-soluble steric stabilizer, if required a porogen, 25 and if required a polymerization initiator and allowing said monomer to diffuse into said seed particles to form an aqueous dispersion of swollen seed particles; and

30 3) initiating polymerization of said monomer in an aqueous dispersion of swollen seed particles,

characterised in that

35 where the mode diameter of said swollen seed particles is greater than 5μm then the aqueous phase of said aqueous dispersion of swollen seed particles during polymerization further contains as a steric stabilizer a water soluble cellulose ether

or in that where said mode diameter of said swollen seed particles is in the range 1 to 25μm the aqueous phase of said aqueous dispersion of swollen seed

- 37 -

particles during polymerization further contains as a steric stabilizer polyvinylpyrrolidone.

2. A process as claimed in claim 1 wherein a polyvinyl pyrrolidone of weight average molecular weight 10 to 5 2000 kD is used as said steric stabilizer.

3. A process as claimed in either of claims 1 and 2 wherein a polyvinyl pyrrolidone is used as a steric 10 stabilizer and the mode diameter of said swollen seed particles is up to 16 $\mu\text{m}$ .

4. A process as claimed in claim 1 wherein, where the aqueous phase of said aqueous dispersion of swollen seed 15 particles during polymerization further contains as a steric stabilizer a water soluble cellulose ether, the mode diameter of said swollen seed particles is greater than 15 $\mu\text{m}$ .

20 5. A process as claimed in claim 1 or claim 4 wherein a hydroxy propylmethyl cellulose is used as a said steric stabilizer.

25 6. A process as claimed in claim 5 wherein said hydroxy propylmethyl cellulose is Methocel K-100.

7. A process as claimed in any one of claims 1, 4, 5 or 6 wherein a cellulose ether of molecular weight 10 to 30 100 kD is used as said steric stabilizer.

8. A process for the preparation of porous monodisperse polymer particles which process comprises:

- 1) either
  - (a) forming an aqueous dispersion comprising (i) monodisperse swellable seed polymer (or oligomer) 35 particles, (ii) droplets comprising an organic compound (e.g. a polymerization initiator) with a molecular

- 38 -

weight below 5000 Dalton and a water solubility at 25°C of less than 10<sup>-2</sup>g/L, (iii) an anionic surfactant, and, optionally, (iv) an organic solvent in which said organic compound is soluble;

5 and (b) allowing said organic compound to diffuse into said seed particles,

or

10 (a) forming an aqueous dispersion comprising monodisperse swellable seed oligomer particles and preferably an anionic surfactant;

15 2) contacting the aqueous dispersion of seed particles with a monomer which, where said organic compound is present, is at least ten times more water soluble than said organic compound, and allowing said monomer to diffuse into said seed particles to form an aqueous dispersion of swollen seed particles and if required adding a water-soluble steric stabilizer, if required adding a porogen, and if required adding a polymerization initiator; and

20 3) initiating polymerization of said monomer in an aqueous dispersion of swollen seed particles, characterised in that said swollen seed particles contain at least two porogens, at least one of which is a solvent for the polymer produced in step (3) and at 25 least one of which is not a solvent for the polymer produced in step (3).

9. A process as claimed in claim 8 wherein said porogen comprises toluene and n-heptane.

30 10. A process for the preparation of monodisperse polymer particles which comprises:

35 1) preparing monodisperse swellable seed particles by emulsion polymerization wherein an anionic surfactant is employed as emulsifier under substantially oxygen-free conditions, said swellable seed particles having a mode particle diameter in the range of 0.2 to

1  $\mu$ m;

2) where said seed particles are non-oligomeric (and optionally where they are oligomeric), (a) contacting said seed particles with an aqueous dispersion comprising an organic compound (e.g. a polymerization initiator) with a molecular weight below 5000 Dalton and a water solubility at 25°C of less than  $10^{-2}$ g/L, an anionic surfactant and, optionally, an organic solvent in which said organic compound is soluble and (b) allowing said organic compound to diffuse into said seed particles;

3) contacting the aqueous dispersion of seed particles with a monomer which, where said organic compound is used, is at least ten times more water soluble than said organic compound, and allowing said monomer to diffuse into said seed particles to form an aqueous dispersion of swollen seed particles, and if required adding a water-soluble steric stabilizer, if required adding a porogen, and if required adding a polymerization initiator; and

4) initiating polymerization of said monomer in an aqueous dispersion containing a steric stabilizer in the continuous phase.

25 11. A process as claimed in claim 10 wherein in step (1) the oxygen content of the aqueous phase is between 0 and 1 ppm.

30 12. A process as claimed in any one of claims 1 to 11 wherein said monomer comprises at least 30% by weight divinyl benzene.

13. A process as claimed in any one of claims 1 to 12 wherein said organic compound is dioctanoyl peroxide.

35 14. A process for the preparation of monodisperse polymer particles which process comprises:

- 40 -

1) either

(a) forming an aqueous dispersion comprising (i) monodisperse swellable seed polymer (or oligomer) particles, (ii) droplets comprising an organic compound (e.g. a polymerization initiator) with a molecular weight below 5000 Dalton and a water solubility at 25°C of less than 10<sup>-2</sup>g/L, (iii) an anionic surfactant, and, optionally, (iv) an organic solvent in which said organic compound is soluble;

10 and (b) allowing said organic compound to diffuse into said seed particles;

or

(a) forming an aqueous dispersion comprising monodisperse swellable seed oligomer particles and preferably an anionic surfactant;

15 2) contacting the aqueous dispersion of seed particles with a monomer which, where said organic compound is present, is at least ten times more water soluble than said organic compound, and allowing said monomer to diffuse into said seed particles to form an aqueous dispersion of swollen seed particles and if required adding a water-soluble steric stabilizer, if required adding a porogen, and if required adding a polymerization initiator; and

20 25 3) initiating polymerization of said monomer in an aqueous dispersion of swollen seed particles, characterised in that said monomer comprises at least two acrylic or methacrylic acid or ester monomers, more preferably at least one being glycidyl methacrylate.

30 15. A process as claimed in claim 12 wherein glycidyl methacrylate is used as a said monomer.

35 16. A process as claimed in any one of claims 1 to 15 wherein, where the monomer is an amino-functionalized monomer (or where two or more monomers are used and one comonomer is an amino functionalized monomer), said

- 41 -

organic compound, if present, is a non-initiator and a polymerization initiator is added after said seed particles have been swollen.

5 17. A process as claimed in claim 16 wherein said non-initiator is dioctyladipate.

10 18. A process as claimed in claim 16 or claim 17 wherein said polymerization initiator is 2,2'-azobis-(2-methylbutyronitrile).

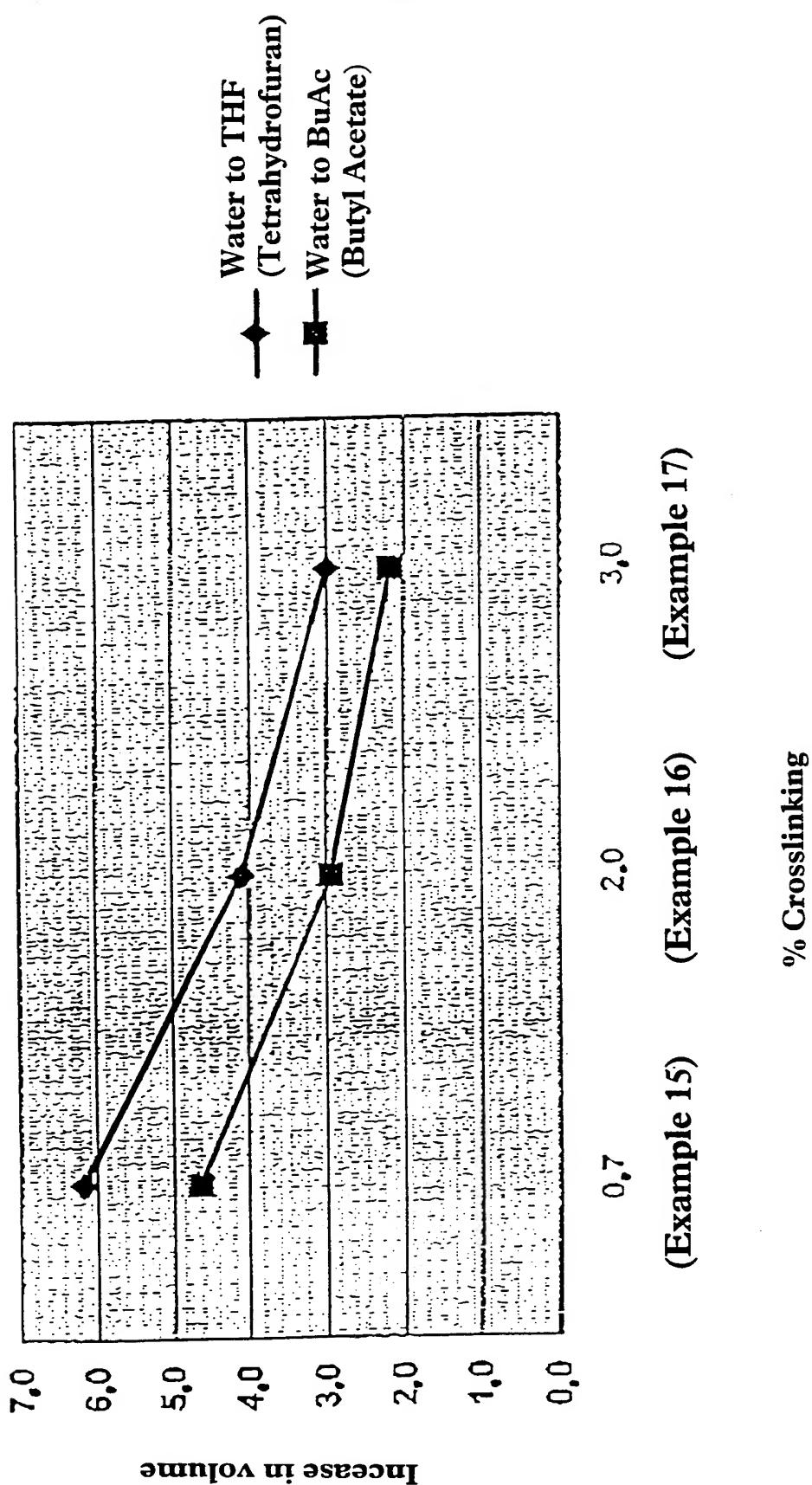
15 19. A process as claimed in any one of claims 1 to 18 wherein said anionic surfactant is sodium dodecyl sulphate.

20 20. A process as claimed in any one of claims 1 to 19 wherein said monodisperse polymer particles are subsequently coated, impregnated or derivatised.

20 21. A method of cleaning monodisperse polymer particles, in particular particles produced by swelling a seed polymer (or oligomer) particle in aqueous dispersion and polymerizing a monomer within the swollen seed particles, which method comprises contacting said monodisperse polymer particles with butyl acetate.

25

Fig. 1



# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 00/01334

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C08F257/02 C08F265/04 C08F291/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C08F A61L C09J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 97 40076 A (BERGE ARVID ; SAETHRE BAARD (NO); UGELSTAD JOHN (NO); JACOBSEN HARA) 30 October 1997 (1997-10-30)</p> <p>* page 4, line 22-27 ; page 3, line 6 – page 4, line 5 ; examples ; page 5, line 23 – page 6, line 6 ; page 9, line 3-8 ; Table 1 ; Tests 1-16 *</p> <p>page 8, line 24-30; claims 1-14</p>	1-8, 10-16, 18-21
X	<p>WO 92 16581 A (CORNELL RES FOUNDATION INC) 1 October 1992 (1992-10-01)</p> <p>* page 7, line 19 – page 10, line 27 ; page 4, line 3 – page 5, line 16 ; page 3, line 4-18 *</p> <p>claims 1-10; examples 1-7</p>	1-3,8-21

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

21 June 2000

Date of mailing of the international search report

28/06/2000

Name and mailing address of the ISA  
European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 000 nl,  
Fax: (+31-70) 340-3016

Authorized officer

Hammond, A

## INTERNATIONAL SEARCH REPORT

Intell.	onal Application No
PCT/GB 00/01334	

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 12167 A (DOW CHEMICAL CO) 24 June 1993 (1993-06-24)  * claims 1-16 * page 7, line 21-25 ----	1,4-8, 10,11, 13,19,20
P,X	WO 99 19375 A (COCKBAIN JULIAN ; DYNOP IND ASA (NO)) 22 April 1999 (1999-04-22) * examples 1-10 * page 4, line 32 -page 6, line 2; claims 1-18 ----	1
X	GB 1 255 237 A (SEKISUI KAGAKU KOGYO KABUSHIKI KAISHA) 1 December 1971 (1971-12-01) claims 1-9; examples 1-8 ----	1
A	WO 93 17055 A (CORNELL RES FOUNDATION INC) 2 September 1993 (1993-09-02) claims 1-11; examples 1-10 -----	1

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/GB 00/01334

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9740076	A 30-10-1997	NO 961625	A	08-12-1997
		AU 2653897	A	12-11-1997
		CA 2252514	A	30-10-1997
		EP 0897397	A	24-02-1999
		PL 329611	A	29-03-1999
		SK 146898	A	11-06-1999
WO 9216581	A 01-10-1992	US 5130343	A	14-07-1992
		AU 1584492	A	21-10-1992
		CA 2106005	A	14-09-1992
		DE 69220214	D	10-07-1997
		DE 69220214	T	04-12-1997
		EP 0575488	A	29-12-1993
		JP 7100746	B	01-11-1995
		JP 7500849	T	26-01-1995
WO 9312167	A 24-06-1993	US 5231115	A	27-07-1993
		CA 2122028	A	24-06-1993
		CN 1073458	A	23-06-1993
		DE 69212162	D	14-08-1996
		DE 69212162	T	21-11-1996
		EP 0617714	A	05-10-1994
		HU 67857	A	29-05-1995
		JP 7502549	T	16-03-1995
WO 9919375	A 22-04-1999	AU 9356598	A	03-05-1999
		JP 11116610	A	27-04-1999
GB 1255237	A 01-12-1971	DE 1917090	A	06-11-1969
		FR 2005711	A	12-12-1969
		NL 6905307	A, B	08-10-1969
WO 9317055	A 02-09-1993	US 5306561	A	26-04-1994
		DE 69303602	D	14-08-1996
		DE 69303602	T	06-03-1997
		EP 0626976	A	07-12-1994
		JP 7504223	T	11-05-1995